UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,204	01/25/2008	Carsten Juergen Kirschning	RSW 86283 US	4608

65159 7590 04/29/2010

TechLaw LLP
10755 Scripps Poway Parkway, Suite 465
San Diego, CA 92131

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
04/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@techlawllp.com
david@techlawllp.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,204	KIRSCHNING ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28,30 and 31* is/are pending in the application.

4a) Of the above claim(s) *31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-31* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 23 September 2009 has been entered in full. Claims 3 and 6 are amended. Claim 29 is cancelled.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-4, 18-22, drawn to a cross-reactive antibody in the reply filed on 16 June 2009 is acknowledged. The traversal is on the ground(s) that the inventors conducted research and tested the only antibody described in Espevik et al. (i.e., TL2.1). Applicant argues that the results of this testing indicate that the TL2.1 monoclonal antibody was not cross-reactive between different mammalian species. Applicant indicates that Espevik does not contain an enabling disclosure regarding a cross-reactive anti-TLR2 antibody as recited in claim 1. This is found persuasive *in part*. After reviewing the instant specification (page 3; Figure 10-14) and post-filing date art (see Abcam technical datasheet attached to the instant Office Action, for example), the Examiner acknowledges that the TL2.1 monoclonal antibody of Espevik binds human TLR2 and not murine TLR2. Thus, Inventions I-IV involve the same or corresponding special technical feature, namely a cross-reactive antibody that binds to the C-terminal portion of the extracellular domains of at least human and murine TLR2. Hence, the restriction requirement between Groups I-IV is *withdrawn* and claims 1-28 are 30 are hereby rejoined. However, the products and methods of Groups I-IV still lack a technical relationship with the method of Group V (claim 31) and are not considered to have unity of invention. The screening method of Group V does not use or produce the cross-reactive

antibody that binds to the C-terminal portion of the extracellular domains of at least human and murine TLR2 of Group I. See 37 CFR 1.475(c).

The requirement is still deemed proper and is therefore made FINAL.

Claim 31 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 23 September 2009.

Claims 1-28 and 30 are under consideration in the instant application.

Specification

1. The abstract of the disclosure is objected to because it uses legal phraseology often used in patent claims, such as "means" and "said," which should be avoided (see lines 5-6).

Correction is required. See MPEP § 608.01(b).

2. The disclosure is objected to because of the following informalities:

2a. The Brief Description of the Drawings for Figures 7-9 does not adequately describe the Figures. The Brief Descriptions appear to be methods/protocols for FACS and immunohistochemistry rather than a concise explanation of the results shown in the Figures.

2a. The Brief Description of the Drawings for Figure 16 does not refer to Figures 16A1-16A3. At pages 22-23, the specification only refers to Figures 16 and 16A. However, there is no Figure 16A. It is noted that the specification's description of "Figure 16A" seems to match the Figure titled "16 A2".

Appropriate correction is required.

Claim Objections

3. Claims 6, 10, 17 are objected to because of the following informalities:

3a. Claim 6 uses the acronym "TLR2" without first defining what it represents in the independent claim. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

3b. In claim 6, line 7, delete the term "for".

3c. In claim 10, line 2, the term "comprising" should be amended to recite "comprises".

3d. In claim 17, the terms "E.coli" and "Bacillus subtilis" should be italicized.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3-28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claims 3-28 and 30 are indefinite because the elements recited in the claims do not constitute proper Markush groups. The claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See claims 3-7, 18, 20, 23, for example. See MPEP § 2173.05(h).

4b. Claim 3 is rejected as being indefinite for recitation of the phrase "variable regions of the heavy- and light chain comprising the amino acid sequence as depicted in SEQ ID NO: 6 and/or 7". It is not clear which SEQ ID NO: refers to the heavy chain and which refer to the light chain.

4c. Claims 5 and 8-17 are rejected as being indefinite because claim 5 recites the limitation "the variable regions of the heavy and/or light chain" in lines 1-2. There is insufficient

antecedent basis for this limitation in the claim. Claim 1, from which claim 5 depends, does not recite "variable regions of the heavy and/or light chain".

4d. Claims 6-7 are rejected as being indefinite because the claim 6 recites " the nucleic acid sequence of SEQ ID NO: 1 and/or2 or its complement and encodes a protein region…". It is not clear how the nucleic acid complement produces the protein region of interest. A complement is a sequence of nucleotide bases in one strand of a DNA or RNA molecule that is exactly complementary (adenine-thymine, adenine-uracil, or guanine-cytosine) to that on another single strand.

4e. Claim 8 is rejected as being indefinite because it is not clear what the phrase "a nucleic acid specifying one or more regulatory sequences operably linked thereto" is intending to encompass. It is not clear what the term "specifying" means in the context of the claim. Does the nucleic acid encode one or more regulatory sequences? Or, does the nucleic acid further comprise one or more regulatory nucleic acid sequences operably linked thereto?

4f. Claims 20-21 are indefinite because the elements recited in claim 20 do not constitute proper Markush groups. For instance, in claim 20, line 2, the claim is missing the phrase "the group consisting of" after "are selected from". See MPEP § 2173.05(h).

4g. The phrase "agents blocking further pattern recognition receptors" in claims 20 and 21 is a relative phrase which renders the claims indefinite. The phrase "agents blocking further pattern recognition receptors" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what receptors and hence, what blocking agents are encompassed by the claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 1-3 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Claims read on a product of nature in that the claimed polynucleotide is not "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty,* 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" as taught by page 24, 3rd full paragraph and page 29 of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: (i) an isolated cross-reactive antibody which inhibits or blocks TLR2-mediated immune cell activation by binding to the C-terminal of the extracellular domains of human and murine TLR2; (ii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 6 (and nucleic acids encoding such); (iii) a variable light chain comprising the amino acid sequence of SEQ ID NO: 7 (and nucleic acids encoding such); (iv) an isolated host cell; (v) a pharmaceutical composition comprising said cross-reactive antibody; and (vi) a

method of preventing or treating TLR2-induced septic shock in a mammal comprising administering to said mammal the isolated cross-reactive antibody, ***does not reasonably provide enablement for*** variants or portions of the heavy chain of SEQ ID NO: 6 and the light chain of SEQ ID NO: 7 (and nucleic acids encoding such); a host; pharmaceutical compositions comprising nucleic acids or a vector; a method of preventing or treating a TLR2 mediated process; and a method of treatment by administering a nucleic acid or vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is directed to a cross-reactive antibody which specifically inhibits or blocks the mammalian TLR2-mediated immune cell activation by specifically binding to the C-terminal portion of the extracellular domains of at least human and murine TLR2. Claim 3 recites that the antibody specifically binds through its variable regions of the heavy and light chain comprising the amino acid sequence as depicted in SEQ ID NO: 6 and/or 7, or a variant thereof. Claim 5 is directed to an isolated nucleic acid coding foe the variable regions of the heavy and/or light chain of the antibody of claim 1. Claim 6 recites an isolated nucleic acid which comprises the sequence of SEQ ID NO and/or 2 or variants thereof that encode a protein region that specifically binds to the C-terminal portion of the extracellular domains of at least human and murine TLR2. Claim 12 recites a host that has been transformed with a vector. Claim 18 recites a pharmaceutical composition comprising an antibody of claim 1, a nucleic acid encoding the variable regions of the heavy and/or light chains of said antibody or a vector comprising said nucleic acid and a pharmaceutically acceptable carrier. Claim 23 recites a method of preventing and/or treating a TLR2-mediated process in a mammal comprising administering the antibody of

claim 1, a nucleic acid encoding the variable regions of the heavy and/or light chains of said antibody, or a vector comprising said nucleic acid. Claim 30 recites that the TLR2-mediated process of claim 23 is selected from rheumatoid arthritis, vascular arthritis, and inflammatory bowel disease.

The specification of the instant application teaches that a cDNA fragment encoding the N-terminal 587 amino acids of mTLR2 was amplified from a RAW264.7 cDNA library (page 29, 2nd full paragraph). The specification discloses that the murine TLR2ECD was fused to a C-terminal thrombin cleavage site followed by a human IgGFcγ moiety. The murine TLR2ECD protein was purified upon overexpression in HEK293 cells and thrombin digestion. A *TLR2*$^{-/-}$ mouse was immunized by intraperitoneal injection of TLR2ECD and a thioated DNA oligonucleotide for three times within eight weeks. Its splenocytes were fused with murine P3X cells and hybridomas were selected and monoclonal antibody specificities for TLR2ECD were analyzed (page 29, 2nd full paragraph). The specification teaches that the antibody, T2.5, immunoprecipitated native murine and human TLR2 (page 24, 3rd full paragraph). T2.5 also inhibited murine and human TLR2 mediated cell activation by TLR2 specific stimuli P_3CSK_4 or *B. subtilis* applied to HEK293 cells overexpressing TLR2, murine RAW264.7, and primary macrophages (bottom of page 24 through the middle of page 25; Figure 3). The specification also discloses that in mice given T2.5 either prior (1h) or up to 2 h after or *B. subtilis* microbial challenge, all or *B. subtilis* challenged mice survived (page 26, bottom of 1st full paragraph; Figure 6b). The specification adds that treatment of T2.5 3 h after potentially lethal injection saved 75% of the mice challenged (page 26, bottom of 1st full paragraph; Figure 6b).

(i) Regarding "portions", "variants", and "parts" of antibodies, amino acids, and nucleic acids (see claims 1, 3, 5, 6, 7, 18, 23 for example only), the specification teaches that "variants" according to the invention especially such nucleic acids which contain one ore more substitutions, insertions and/or deletions when compared to the nucleic acids of SEQ ID NO: 1 and 2 (page 12, 1st full paragraph). The specification discloses that nucleic acids can show for example at least about 80%, more typically at least about 90% or 95% sequence identity to the nucleic acids described in SEQ ID NO: 1 and 2 (page 12, 2nd full paragraph). The specification teaches that also contemplated are amino acid sequences which encompass all sequences differing from the herein disclosed sequences by amino acid insertions, deletions, and substitutions (page 13, 2nd through 4th paragraphs). However, the specification does not teach any variant or part of the polypeptides and nucleic acids other than the full-length amino acid sequences of SEQ ID NOs: 6 and 7 and the full-length nucleic acid sequences of SEQ ID NOs: 1 and 2. The specification also does not teach any C-terminal "portions" of the extracellular domains of human and murine TLR2, other than full-length (see claim 1, for example). The specification does not teach functional or structural characteristics of the amino acid and nucleic acid variants, fragments, parts, and portions recited in the claims.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various

sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Additionally, Lederman et al. (Mol Immunol 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al. (Proc Natl Acad Sci USA 77: 3211-3214, 1980) also disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Daniel et al. (Virology 202: 540-549, 1994) also

disclose that primary amino acid sequences do not predict antigenic determinants and therefore, changing the amino acid sequence of a polypeptide may also affect antigenicity (pg 540, 547). Because of this lack of guidance in the instant specification, the extended experimentation that would be required to determine which amino acid sequences and modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (see Ngo et al., for example), it would require an undue amount of experimentation for one of skill in the art to arrive at the large number of C-terminal portions of the extracellular domains of human and/or murine TLR2 and antibodies generated against such.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(ii) Regarding claims 12-14, the Examiner has interpreted the claims as reading on isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that the antibody/antibody fragment can be produced in transgenic animals (page 14, 5th full paragraph).

However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated nucleic acid of SEQ ID NO: 1 or 2. The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention.

The specification also discloses that the present invention "is directed to a gene therapy approach for use in the treatment of chronic diseases. The approach basically follows the already known protocols for gene therapy and comprises in particular the step of cloning a sequence comprising the variable domains of the antibody of the invention as specified above into an expression vector and introducing said expression vector into a host, for example a human patient in order to cause an overexpression of said antibody/antibody fragment in said patient" (page 17, 1st paragraph). However, the specification does not teach any methods or working examples that indicate a heavy or light chain nucleic acid of SEQ ID NO: 1 or 2 (or a vector comprising such) is introduced and expressed in a cell for therapeutic purposes. The disclosure

in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the nucleic acids into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express a nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a nucleic acid molecule of SEQ ID NO: 1 or 2 in the cell of an organism or be able to produce a protein in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the heavy or light chain protein and to introduce and express a heavy chain or light chain nucleic acid in a cell of an organism for therapy; the lack of direction/guidance presented in the specification regarding how to introduce a nucleic acid in the cell of an organism to be able produce that protein; the absence of working examples directed to same; the complex nature

of the invention; the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells; and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated host cell…").

(iii) At page 16, last paragraph, the specification teaches that the antibody, nucleic acid, vector or composition of the invention are used in the prevention and/or treatment of inflammatory processes or any other process induced by bacterial infection, trauma, or chronic inflammation. The specification also adds that the they can be used for the prevention and/or treatment of bacteriaemia or sepsis, rheumatoid arthritis, vascular arthritis, or inflammatory bowel disease. As mentioned previously, the specification only discloses that in mice given T2.5 either prior (1h) or up to 2 h after or *B. subtilis* microbial challenge, all or *B. subtilis* challenged mice survived (page 26, bottom of 1st full paragraph; Figure 6b). The specification adds that treatment of T2.5 3 h after potentially lethal injection saved 75% of the mice challenged (page 26, bottom of 1st full paragraph; Figure 6b). However, the specification does not teach any methods or working examples that indicate that TLR2 cross-reactive antibodies, nucleic acids, or vectors prevent or treat all TLR2-mediated processes (including rheumatoid arthritis, vascular arthritis, and inflammatory bowel disease), other than TLR2-driven septic shock. Relevant literature teaches that the role of TLR2 in many diseases or conditions is not certain or predictable. For example, McCormack et al. disclose that elevated levels of TLR2 have been found in macrophages isolated from rheumatoid arthritis synovium (Arthritis Res Therapy 11(5):

243, 2009;; page 244, column 2, 2nd paragraph). However, McCormack et al. also disclose that IL1rn-/-TLR2-/- animals develop severe arthritis, suggesting an anti-inflammatory role for TLR2 in that model (page 244, column 2, 3rd full paragraph). McCormack et al. state that the anti-inflammatory nature of TLR2 in the IL1-receptor antagonist knockout model is in contrast to results obtained in a streptococcal cell wall induced model of arthritis, where mice deficient for TLR2 have reduced severity of arthritis (page 244, column 2, 3rd full paragraph). Cario, E. also teaches that deficient TLR2 signaling may imbalance commensal-dependent intestinal epithelial barrier defense, facilitating mucosal injury and leading to increased susceptibility to colitis (Mucosal Immunol 1(Suppl 1): S62-S66, 2008; abstract). Specifically, Cario discloses that loss of TLR2 leads to exacerbation of intestinal inflammation in DSS colitis with high morbidity and mortality (page S64, bottom of column 1 through column 2). Cario indicates that treatment with a synthetic TLR2 ligand significantly suppresses mucosal inflammation *in vivo* (page S64, column 2, last paragraph). Hence, in view of the lack of guidance in the instant specification and the contradictory state of the art, there is no clear nexus or mechanism between TLR2 and TLR2-mediated processes, other than TLR2-induced septic shock. A large quantity of experimentation would be required of the skilled artisan to identify the nexus between TLR2 and all TLR2-mediated processes and administer cross-reactive antibodies, nucleic acids, or vectors for prevention or treatment. Such experimentation is considered undue. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970);

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily prevent or treat all possible TLR2-mediated processes in a mammal by administering cross-reactive TLR2 antibodies, nucleic acids, or vectors. It is also noted that the specification does not teach any methods or working examples that indicate a heavy or light chain nucleic acid of SEQ ID NO: 1 or 2 (or a vector comprising such) is introduced and expressed in a cell for therapeutic purposes (please see section (ii) above).

Due to the large quantity of experimentation to treat all possible TLR2-mediated processes; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

7. Claims 1-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to a cross-reactive antibody which specifically inhibits or blocks the mammalian TLR2-mediated immune cell activation by specifically binding to the C-terminal portion of the extracellular domains of at least human and murine TLR2. Claim 3 recites that the

antibody specifically binds through its variable regions of the heavy and light chain comprising the amino acid sequence as depicted in SEQ ID NO: 6 and/or 7, or a variant thereof. Claim 5 is directed to an isolated nucleic acid coding foe the variable regions of the heavy and/or light chain of the antibody of claim 1. Claim 6 recites an isolated nucleic acid which comprises the sequence of SEQ ID NO and/or 2 or variants thereof that encode a protein region that specifically binds to the C-terminal portion of the extracellular domains of at least human and murine TLR2. Claim 12 recites a host that has been transformed with a vector. Claim 18 recites a pharmaceutical composition comprising an antibody of claim 1, a nucleic acid encoding the variable regions of the heavy and/or light chains of said antibody or a vector comprising said nucleic acid and a pharmaceutically acceptable carrier.

Regarding "portions", "variants", and "parts" of antibodies, amino acids, and nucleic acids (see claims 1, 3, 5, 6, 7, 18, 23 for example only), the specification teaches that "variants" according to the invention especially such nucleic acids which contain one ore more substitutions, insertions and/or deletions when compared to the nucleic acids of SEQ ID NO: 1 and 2 (page 12, 1st full paragraph). The specification discloses that nucleic acids can show for example at least about 80%, more typically at least about 90% or 95% sequence identity to the nucleic acids described in SEQ ID NO: 1 and 2 (page 12, 2nd full paragraph). The specification teaches that also contemplated are amino acid sequences which encompass all sequences differing from the herein disclosed sequences by amino acid insertions, deletions, and substitutions (page 13, 2nd through 4th paragraphs). However, the claims do not require that the C-terminal portion of the extracellular domain and variants and parts of the variable regions of the heavy and light chain amino acid sequences of SEQ ID NO: 6 or 7 or the nucleic acid

sequences of SEQ ID NO: 1 or 2 possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus antibodies generated against a genus of TLR2 C-terminal extracellular domain fragments, a genus of fragments and variants of SEQ ID NOs: 1, 2, 6, and 7, and methods of using such.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include actual reduction to practice, disclosure of drawings or structure chemical formulas, sufficient relevant identifying characteristics (such as, complete or partial structure, physical and/or chemical properties, and functional characteristics when coupled with a known or disclosed structure/function correlation), methods of making the claimed product, level of skill and knowledge in the art, predictability in the art, or any combination thereof. However, in this case, the specification fails to disclose and there is no art-recognized correlation between the structure and function of the genus of TLR2 C-terminal extracellular domain fragments and the genus of fragments and variants of the amino acid sequences of SEQ ID NOs: 6 and 7 and the nucleic acid sequences of SEQ ID NOs: 1 and 2. The specification does not teach which amino acids or nucleic acids can vary and still result in an antibody that cross-reacts with human and murine TLR2. Additionally, the description of one cross-reactive TLR2 antibody (T2.5) is not adequate written description of an entire genus of functionally equivalent antibodies, variable regions of the heavy and light chains (and nucleic acids encoding such), and methods of using such which incorporate all "portions", "variants", and "parts" with all possible biological functions.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

Thus, the skilled artisan cannot envision the detailed chemical structure of the antibodies generated against TLR2 C-terminal extracellular domain fragments and fragments and variants of SEQ ID NOs: 1, 2, 6, and 7 of the encompassed claims, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the full breadth of the claims does not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Elson, G. US 2005/0265998 (TLR4 neutralizing antibodies)

Elson, G. US 2006/0165686 (TLR2 neutralizing antibodies; Figures 19-20; SEQ ID NOs: 54, 56, 57, and 59)

Lifespan Biosciences technical datasheet for LS-C90537 (polyclonal antibody raised against the extracellular domain of mouse TLR2 (amino acids 564-580 and 751-770))

Uniprot Accession No. Q9QUN7; modified 23 March 2010 (mouse TLR2 sequence and domains)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
15 April 2010

/Bridget E Bunner/
Primary Examiner, Art Unit 1647